Complete Summary

GUIDELINE TITLE

Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Imrie K, Stevens A, Meyer R, Hematology Disease Site Group. Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Dec 22. 46 p. (Evidence-based series; no. 6-8). [65 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Lymphoma and chronic lymphocytic leukemia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

Lymphoma

- To evaluate whether rituximab used alone or in combination with chemotherapy is more effective than non-rituximab-containing regimens for improving overall survival, disease control (as assessed by measures such as progression-free survival, event-free survival, time-to-treatment failure, or response duration), response rate, or quality of life in patients with lymphoma of any type or stage
- To evaluate the toxicity associated with the use of rituximab used alone or in combination with chemotherapy compared with non-rituximab-containing regimens
- To evaluate which patients with lymphoma are more or less likely to benefit from treatment with rituximab compared with those treated with non-rituximab--containing regimens

Chronic Lymphocytic Leukemia (CLL)

- To evaluate what beneficial outcomes are associated with the use of rituximab for the treatment of patients with chronic lymphocytic leukemia
- To evaluate the toxicity associated with the use of rituximab
- To evaluate which patients are more or less likely to benefit from treatment with rituximab

TARGET POPULATION

Lymphoma

Adult patients with lymphoma of any type, at any stage, and any histology

Chronic Lymphocytic Leukemia (CLL)

Adult patients with chronic lymphocytic leukemia at any stage

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

Rituximab monotherapy or combination therapy

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Disease control, as assessed by measures such as:
    - Progression-free survival
    - Event-free survival
    - Time to treatment failure
    - Response duration
- Response rate
- Quality of life
- Toxicity of rituximab alone or in combination with chemotherapy

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Lymphoma

MEDLINE® In-Process & Other Non-Indexed Citations (Ovid) (December 12, 2003), MEDLINE (Ovid) (1966 through August week two, 2005), HealthStar (Ovid) (1975 through November 2003, limited to nonMEDLINE), EMBASE (1980 through August [week 34] 2005), CINAHL (Ovid) (1982 through December 2003), and the Cochrane Library (2005, Issue 3) databases were searched. In MEDLINE, "Exp lymphoma/" (Medical subject heading [MeSH]) was combined with "exp lymphoma, large-cell/" (MeSH), "lymphoma.mp." (textword), and each of the following phrases used as text words: "rituxan.mp.," "rituximab.mp.," "ritux:.mp.," "idec.mp." combined with "c2b8.mp." or "c2b?.mp.," "anti - cd20.mp.," "anticd-20.mp.," "anticd20.mp.," "mabthera.mp.," and "rituxin.mp." These terms were then combined with the search terms for the following publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, randomized controlled trials, controlled clinical trials, and clinical trials. Searches in the other bibliographic databases were similar. The MEDLINE search focused on retrieving randomized controlled trials.

In addition, conference proceedings of American Society of Hematologists (ASH) (1998-2004) and the American Society of Clinical Oncology (ASCO; 1997-2005) were searched for abstracts of relevant trials. Personal files were also consulted.

Relevant bibliographic citations were selected by two reviewers. All the evidence was reviewed by two reviewers.

Chronic Lymphocytic Leukemia (CLL)

MEDLINE (Ovid) (1966 through August week 2, 2005), EMBASE (1980 through August [week 34] 2005), MEDLINE® In-Process & Other Non-Indexed Citations (Ovid) (January 10, 2003), CANCERLIT (Ovid) (1975 through October 2002, limited to nonMEDLINE), HealthStar (OVID) (1975 through October 2002, limited to nonMEDLINE), CINAHL (1982 through December 2002), and the Cochrane Library (Ovid) (2002, Issue 4; the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews were searched) databases were searched. In MEDLINE, "Leukemia, lymphocytic/" (MeSH) was combined with "exp leukemia, lymphocytic, chronic/" (MeSH), "chronic lymphocytic leukemia.mp." (textword), "chronic lymphocytic leukaemia.mp.," "CLL.mp.," and each of the following phrases used as textwords: "rituxan.mp.," "rituximab.mp.," "ritux:.mp.," "idec.mp." combined with "c2b8.mp." or "c2b?.mp.," "anti -cd20.mp.," "anticd-20.mp.," "anticd20.mp.," and "mabthera.mp.". Searches in the other bibliographic databases were similar.

In addition, conference proceedings of American Society of Hematologists (1996-2004) and American Society of Clinical Oncology (1995-2005) were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearinghouse (http://www.guideline.gov) were also searched for existing evidence -based practice guidelines. Personal files were also reviewed.

Relevant bibliographic citations were selected by two reviewers in the original literature search. Evidence was reviewed by two reviewers.

Study Selection Criteria

Inclusion Criteria

Lymphoma

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts in the English language of:

1. Randomized controlled trials, systematic reviews, meta-analyses, or evidence-based practice guidelines
2. Studies that include adult patients with lymphoma of any type, at any stage, and any histology
3. Studies comparing rituximab alone with non-rituximab regimens or comparing rituximab combination therapy with non-rituximab regimens
4. Studies evaluating one or more of the following outcomes: overall survival, disease control (progression-free survival, event-free survival, time-to-treatment failure, or response duration), response rate, quality of life, or toxicity.

CLL

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts in the English language of:

1. Primary studies of any design type, systematic reviews, meta-analyses, or evidence-based clinical practice guidelines
2. Studies that include patients with CLL or small lymphocytic lymphoma (SLL). For studies including patients with various histologic subtypes of lymphoproliferative disorders, outcomes of patients with CLL must be identified separately.
3. Studies evaluating rituximab alone or in combination with other agents
4. Studies evaluating at least one of the following outcomes were reported: overall survival, disease control (progression-free survival, time-to-treatment failure, event-free survival, or response duration), or toxicity. If response rate is reported, at least one of the above outcomes must also be reported to be included.

Exclusion Criteria

Lymphoma

Letters, comments, books, notes, and editorial publication types were not considered.

CLL

The following were not considered:

1. Letters, comments, and editorial publication types
2. Reports evaluating patients undergoing stem cell transplantation
3. Studies with fewer than 10 patients

Article Selection

Lymphoma

Citations in the original literature search were reviewed by two reviewers for inclusion. Citations were not blinded for author, journal name, institution, or results. Each citation was scored as: "Yes" (inclusion criteria were met, no exclusion criteria were met), "No" (one or more exclusion criteria were met), or "Maybe" (unclear from the citation if article meets any criteria). The full-length article was retrieved if the citation was scored "yes" or "maybe" by at least one reviewer, and inclusion and exclusion criteria were applied to the full article, if necessary. Inter-observer kappa coefficients were calculated using GraphPad QuickCalcs © (GraphPad Software, Inc.) (http://graphpad.com/quickcalcs/kappa1.cfm).

CLL

Citations in the original literature search were reviewed by two reviewers for inclusion. Citations were not blinded for author, journal name, institution, or results. Each citation was scored as: "Yes" (inclusion criteria were met, no exclusion criteria were met), "No" (one or more exclusion criteria were met), or "Maybe" (unclear from the citation if article meets any criteria). The full-length article was retrieved if the citation was scored "yes" or "maybe" by at least one

reviewer, and inclusion and exclusion criteria were applied to the full article, if necessary. Interobserver kappa coefficients were calculated using GraphPad QuickCalcs © (GraphPad Software, Inc.) (http://graphpad.com/quickcalcs/kappa1.cfm).

NUMBER OF SOURCE DOCUMENTS

Systematic Reviews

Two systematic reviews were identified.

Lymphoma

Nineteen retrievable trials were identified.

Chronic Lymphocytic Leukemia

Thirty publications (27 trials) were eligible for inclusion and review.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Lymphoma

The Disease Site Group (DSG) identified that a meta-analysis of the published evidence for this topic is a high priority. However, sufficient information to allow for a meta-analysis is currently unavailable in the published abstracts. The authors will consider conducting a meta-analysis in a future update of this guideline using Review Manager 4.2 (RevMan Analyses), which is available through the Cochrane Collaboration.

Chronic Lymphocytic Leukemia

Data appropriate for meta-analysis were not identified.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Hematology Disease Site Group (DSG) applies a number of principles in its deliberations when evaluating new therapies:

1. An emphasis on randomized controlled trials
2. Recognition of the limitations of data in abstract form
3. The recognition of a hierarchy of outcomes that should influence treatment decisions, with priority given to therapies found to extend life or improve quality of life
4. The influence of disease histology
5. The need to evaluate the generalizability of results to other populations

Diffuse Large Cell Lymphoma

Four trials have evaluated rituximab when combined with anthracycline-based chemotherapy in patients with diffuse large B-cell lymphoma (DLBCL). Two of the trials restricted eligibility to older patients (aged 60 years or greater). In both those trials, the duration of disease control was superior in patients allocated to receive rituximab. Coiffier et al also observed a clinically important and statistically significant difference in overall survival. Habermann et al detected no difference in overall survival. The design and analysis of that trial was complex because it included a second randomization to maintenance therapy with rituximab or observation; a difference in time-to-treatment failure favouring the treatment with maintenance rituximab was observed. A secondary analysis was performed to evaluate the role of maintenance rituximab in populations who received or did not receive rituximab with induction therapy. A difference in time-to-treatment failure was not detected in patients receiving rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) as part of their induction treatment, whereas a significant prolongation of time-to-treatment failure was observed in patients who did not receive rituximab with induction. In younger patients with favourable risk disease, Pfreundschuh et al observed a clinically important and statistically significant prolonged survival and time-to-treatment failure when rituximab was added to CHOP or a CHOP-like regimen.

The Disease Site Group (DSG) has interpreted those results as strongly supporting a role for rituximab in the primary treatment of patients with DLBCL. This interpretation is based on the consistent observation of a longer duration of disease control in patients receiving rituximab and the demonstrated survival advantage reported by Coiffier et al and Pfreundschuh et al. The failure by Habermann et al to detect an overall survival advantage may in part be due to the trial design; the successful use of rituximab as a maintenance therapy in patients who did not receive the drug as part of their induction therapy may have reduced the ability to detect a survival advantage.

The evaluation by Kaplan et al of rituximab in patients with human immunodeficiency virus (HIV)-related lymphoma failed to detect differences between randomized groups with respect to any outcome measure, with the exception of deaths due to infection, which were greater in patients receiving rituximab. Those results suggest that the disease process in patients with HIV-related lymphoma differs from that in patients with lymphoma not associated with

HIV. Greater difficulties in obtaining and maintaining disease control and the increased risks of infectious complications, which in theory might be exacerbated by the reduction in antibody levels associated with rituximab, make the HIV patient group unique.

The DSG considered the data of Haioun et al evaluating rituximab as maintenance therapy following autologous stem cell transplantation too preliminary to form conclusions.

The DSG deliberated over the role of rituximab in salvage therapy of DLBCL and its variants. The systematic review did not identify any randomized trials evaluating the addition of rituximab, however the DSG members were aware of small uncontrolled phase II trials reporting outcomes of patients receiving rituximab containing salvage regimens. These data are difficult to interpret given the small number of patients included, patient selection, and variable number of patients previously exposed to rituximab during primary therapy. Given these limitations, the DSG considered that there is insufficient evidence at this time to support or refute treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated for DLBCL or a variant of DLBCL.

Follicular and Other Low-Grade Lymphomas

Seven trials have tested the addition of rituximab to chemotherapy as a first-line therapy in patients with follicular and other indolent lymphomas. Because two of the trials included patients with mantle cell lymphoma, discussion of this histology has been included in this section. One of those reports is very preliminary and does not include results for the duration of disease control or overall survival and was not considered further. The remaining trials all report large differences in disease control with no increase in major toxicity. Overall survival is reported only in the single fully published paper and was not increased in the rituximab arm at a median follow-up of 30 months. In its deliberations, the DSG recognized that survival or quality of life are not observed to be improved with the addition of rituximab to first-line therapy. The site group was influenced by the magnitude of the benefit in disease control (a 15-month delay in time to re-treatment in the rituximab plus cyclophosphamide, vincristine, and prednisone [R-CVP] trial for example), the lack of significant toxicity, and the survival benefit observed with the addition of rituximab in two different patient populations: DLBCL in first-line, and second-line therapy of follicular and other indolent lymphomas (see below). Furthermore, given the inclusion of a number of non-follicular indolent histologies in three of the seven trials and the comparable activity of rituximab in follicular lymphoma and other non-follicular indolent histologies (excluding small lymphocytic lymphoma/chronic lymphocytic leukemia), the DSG recommends that data from follicular lymphoma be generalized to these histologies. For these reasons the DSG recommends that previously untreated patients with follicular or other indolent B-cell–histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive this chemotherapy in combination with rituximab. Rituximab should be administered at a dose of 375 mg/m^2 and given at the beginning of each treatment cycle of chemotherapy.

The DSG also considered the role of rituximab beyond first-line therapy. For previously treated patients with follicular or other indolent B-cell–histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding small lymphocytic lymphoma, who are appropriate candidates for chemotherapy and who have not previously received rituximab, should receive this chemotherapy in combination with rituximab. This recommendation is based on the improved survival and time to progression observed with the addition of rituximab to fludarabine-cyclophosphamide-mitoxantrone (FCM) reported by Forstpointner et al and Dreyling et al and the improved time to progression reported in the study of CHOP +/-rituximab by Van Oers et al.

The role of rituximab in combination with chemotherapy for patients previously treated with rituximab (alone or in combination) is much less clearly defined. None of the randomized trials included patients who had previously received rituximab. The DSG is unable to offer definitive recommendations where no direct evidence exists but recognizes the need of practitioners and policy-makers for guidance in this situation. The addition of rituximab to chemotherapy in patients beyond first-line treatment is associated with improved time to progression, and, in one trial, survival. The re-use of therapies that have previously been effective for a given patient is a common strategy when managing patients with indolent lymphomas. Data from trials of rituximab monotherapy suggest that in a selected population of rituximab-sensitive patients, a response rate comparable to that observed in first-line treatment can be observed. Cumulative toxicity from multiple treatments with rituximab is not expected, given the lack of myelosuppression observed with this agent and the experience with it in the maintenance setting. Based upon this data, and the consensus of the members of the Hematology DSG, the group recommends that patients previously treated with rituximab who remain sensitive to this agent, and who are appropriate candidates, should receive chemotherapy in combination with rituximab. While no evidence-based definition of rituximab sensitivity exists, the DSG considers relapse one year or more after treatment with rituximab to be a reasonable threshold.

With respect to maintenance therapy, the DSG recognized that four trials reported superior disease control in patients receiving rituximab maintenance following chemotherapy alone or rituximab monotherapy. In one trial, no ultimate improvement in disease control was observed with maintenance therapy in comparison with retreating patients with rituximab at disease progression; other trials did not evaluate 'duration of rituximab benefit' as an outcome measure. Only one trial of maintenance rituximab after combination chemotherapy has been reported. The authors initially randomized patients to treatment with fludarabine-cyclophosphamide-mitoxantrone (FCM) or to FCM plus rituximab. Patients with a complete or partial response were randomized to maintenance therapy or to observation. The results of that trial are preliminary and have been published in abstract form only. The DSG concluded that those data were insufficient to support or refute a recommendation to use maintenance therapy.

Chronic Lymphocytic Leukemia

The data describing the treatment of patients with chronic lymphocytic leukemia (CLL) with rituximab consist mainly of phase II studies plus two historical cohort comparisons. Those study designs are susceptible to the biases of case selection

and to uncertainties with respect to the incremental benefit that might be seen in comparison with a control group. The results of randomized controlled trials have not been reported. The data reviewed were considered to be insufficient to support or refute a recommendation to treat these patients with rituximab. The DSG also considered whether the data for treating patients with lymphoma could be generalized to those with CLL. As indicated in the original publication of Evidence Summary Report #6-8, rituximab appears to be associated with an inferior response rate in CLL in comparison with that seen when the drug is used as a single agent to treat patients with follicular and other low-grade lymphomas. The DSG concluded that the recommendations for using rituximab in patients with CLL would therefore require the results to be from randomized trials.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review

Based on the evidence and the draft recommendations, feedback was sought from Ontario clinicians. Practitioner feedback was obtained through a mailed survey of 120 practitioners in Ontario (60 hematologists, 30 academic medical oncologists, and 30 community medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on August 9, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again).

Practice Guideline Coordinating Committee Approval Process

The evidence-based series was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Eight of 13 members of the PGCC returned ballots. One of the eight members that returned ballots is a member of the Hematology DSG and was therefore not eligible to comment on the evidence -based series. Five members approved the evidence -based series as written, one member approved the guideline and provided suggestions for consideration by the Hematology DSG, and one member approved the guideline conditional on the Hematology DSG addressing specific concerns.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Lymphoma

- Previously untreated patients with diffuse large B-cell lymphoma (DLBCL), or a variant of DLBCL (such as mediastinal sclerosing B-cell lymphoma, T-cell-rich B-cell lymphoma, Burkitt-like lymphoma, or intravascular lymphoma), who are candidates for treatment with curative intent and will receive cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), should receive this therapy in combination with rituximab. This grouping includes patients with untreated DLBCL that has transformed from follicular or other indolent lymphoma.
- There is insufficient evidence at this time to support or refute treatment with a rituximab-containing chemotherapy regimen in patients who have been previously treated for diffuse DLBCL or a variant of DLBCL.
- There is insufficient evidence to support combining rituximab with chemotherapy when treating patients with human immunodeficiency virus (HIV)-related lymphoma. These patients may be at an increased risk for life-threatening infections when rituximab is combined with CHOP.
- Previously untreated patients with follicular or other indolent B-cell-histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding small lymphocytic lymphoma (SLL), who are appropriate candidates for chemotherapy, should receive this chemotherapy in combination with rituximab.
- For previously treated patients with follicular or other indolent B-cell-histology lymphoma (such as mantle cell lymphoma, marginal zone lymphoma, and lymphoplasmacytoid lymphoma), excluding small lymphocytic lymphoma (SLL):
    - Patients who have not previously received rituximab and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab.
    - Patients who have previously received rituximab and who have achieved a response of at least one year's duration to the last rituximab administration and who are appropriate candidates for chemotherapy should receive this chemotherapy in combination with rituximab.
- There is currently insufficient evidence to support or refute the additional use of rituximab as a maintenance therapy in patients who have completed chemotherapy plus rituximab.

Chronic Lymphocytic Leukemia (CLL)

- There is insufficient evidence at this time to support or refute the use of single-agent rituximab or a rituximab-containing chemotherapy regimen in patients with chronic lymphocytic leukemia (CLL).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- In one randomized trial comparing cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab (CHOP-rituximab) with CHOP alone in previously untreated patients with diffuse large B-cell lymphoma (DLBCL) (aged 60 to 80 years), complete response, disease control (event-free survival), and overall survival were superior in patients allocated to receive CHOP-rituximab. In another randomized trial (reported in abstract form) that compared CHOP-like chemotherapy to the same chemotherapy with rituximab in patients with previously untreated DLBCL, complete response, disease control (time-to-treatment failure), and overall survival were superior in patients that received rituximab in addition to chemotherapy compared to patients that received chemotherapy alone.
- In one randomized trial comparing CHOP-rituximab with CHOP alone, in previously untreated patients with diffuse large B-cell lymphoma (age 60 years and greater), disease control (time-to-treatment failure) was superior in patients allocated to receive CHOP-rituximab. No difference between randomized groups in overall survival was detected. In that trial, patients responding to induction therapy underwent a second randomization to receive maintenance therapy with rituximab or to be observed. Disease control (time-to-treatment failure) was superior in patients allocated to receive rituximab; no difference between randomized groups in overall survival was detected.
- In three trials comparing chemotherapy with or without rituximab in previously untreated patients with follicular lymphoma, disease control (time-to-treatment failure, time to progression, or two-year event-free survival) was superior in patients allocated to receive rituximab. Overall survival results were reported for only one trial; no significant difference was observed for 30-month overall survival.
- In one trial comparing chemotherapy with or without rituximab in previously treated patients with indolent lymphomas, response rate, disease control (progression-free survival) and overall survival were superior in patients allocated to receive rituximab. In another trial comparing CHOP to CHOP-R in patients with follicular lymphoma relapsed or resistant to a maximum of two non-anthracycline regimens, complete response and disease control (three-year progression-free survival) were superior in patients allocated to receive CHOP-R compared to patients that received CHOP alone.
- There were no trials that compared chemotherapy to the same chemotherapy plus rituximab in patients who had previously received rituximab and achieved a response of at least one year's duration. Two randomized trials comparing chemotherapy plus rituximab to chemotherapy alone in patients previously treated with rituximab alone showed improvement in survival or progression-free survival. One randomized trial that compared maintenance rituximab to re-treatment with rituximab at disease progression following

induction treatment with rituximab monotherapy, reported a response rate for re-treatment that was comparable to first-line treatment. In addition, a non-comparative trial of rituximab monotherapy in rituximab-sensitive patients demonstrated comparable response rates to that observed for first-line treatment.
- No important additional hematologic or non-hematologic toxicities were observed when rituximab was combined with chemotherapy.

POTENTIAL HARMS

Lymphoma

The authors have previously summarized treatment-related toxicity with single-agent rituximab; in general, this treatment is well tolerated with frequent, but rarely severe, infusional toxicities observed. The majority of adverse events occurred with the first infusion.

Chronic Lymphocytic Leukemia

The chronic lymphocytic leukemia (CLL) monotherapy reports described toxicities that were similar to those previously summarized with single-agent rituximab. Again, treatment was well tolerated with frequent, but rarely severe, infusional toxicities observed.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Rituximab has a favourable single-agent toxicity profile. The addition of rituximab to chemotherapeutic regimens such as cyclophosphamide, vincristine, and prednisone (CVP), cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and fludarabine, cyclophosphamide, and mitoxantrone (FCM) does not appear to significantly alter the toxicity of these regimens in lymphoma.
- Rituximab should be administered at a dose of 375 mg/m^2 and given at the beginning of each treatment cycle of chemotherapy.
- In the absence of randomized data evaluating the role of rituximab re-treatment, the recommendation that rituximab be reused in combination with chemotherapy is based on the consensus opinion of the Hematology Disease Site Group.
- There is a rapid availability of new data regarding the role of rituximab in treating these diseases. Practitioners and patients are advised to review the Web site of Cancer Care Ontario's Program in Evidence-based Care (PEBC) to learn the status of this practice guideline.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding their content or use or application and disclaims any for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Not Stated

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Imrie K, Stevens A, Meyer R, Hematology Disease Site Group. Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2005 Dec 22. 46 p. (Evidence-based series; no. 6-8). [65 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2005 Feb 17 (revised 2005 Dec 22)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The members of the Hematology Disease Site Group (DSG) disclosed potential conflicts of interest relating to the topic of this practice guideline. The lead author and citation and evidence reviewer (KI) of this topic was a co -investigator in one trial included in this report and is involved with an ongoing trial on rituximab. Three other DSG members reported research involvement with trials on this topic, of which one member was involved with one trial in this report. In addition, three of the above DSG members, including the lead author, reported involvement with the pharmaceutical company that manufactures rituximab, including research funding, membership on boards of directors or advisory committees, provision of consultancy, or honoraria.

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Rituximab in lymphoma and chronic lymphocytic leukemia: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2005 Dec 22.

Various p. (Practice guideline; no. 6-8). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on August 11, 2005. The information was verified by the guideline developer on September 16, 2005. This NGC summary was updated by ECRI on August 18, 2006. The updated information was verified by the guideline developer on August 23, 2006.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

Date Modified: 9/25/2006